PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 27 November 2000 (27.11.00)	
International application No. PCT/SE00/00755	**Applicant's or agent's file reference** H 2036-1 WO
International filing date (day/month/year) 19 April 2000 (19.04.00)	**Priority date** (day/month/year) 19 April 1999 (19.04.99)
Applicant ABRAHAMSSON, Bertil et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

30 October 2000 (30.10.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Charlotte ENGER
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

K 09/581967

PATENT COOPERATION TREATY

PCT

REC'D 30 AUG 2001
WIPO

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
H 2036-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE00/00755	19.04.2000	19.04.1999
International Patent Classification (IPC) or national classification and IPC7		
A61K 45/00, A61K 9/20, A61P 3/06		
Applicant		
AstraZeneca Aktiebolag et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.10.2000	22.08.2001
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Authorized officer Anna Sjölund/EÖ Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/00755

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☐ the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement) under article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/00755

III. Non-establishment f opinion with regard t novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11-15,20,22-23

because:

☒ the said international application, or the said claims Nos. 11-15,20,22-23
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard t n velty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-10, 16-19, 21	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-10, 16-19, 21	NO
Industrial applicability (IA)	Claims	1-10, 16-19, 21	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Following documents are cited in this report:
D1: US 5723458 A1
D2: US 5614220 A1
D3: Dialog , File Embase, 02888148, Embase No 1985132107, Jacobsen et al., British Medical Journal 1985, 290/6478, 1315-1318

The subject matter of claims 1-10 refers to oral pharmaceutical formulations comprising an inhibitor compound of the ileal bile acid transport (IBAT inhibitor compound). The formulation is designed to deliver the IBAT inhibitor compound in the ileum.
Present claims 1-10 are defined by reference to the desirable effect of the formulation, such as the target for delivery of the active substance or the lag time. The claims lack the technical features needed to bring about such effects. In the same claims 1-10 is included the expression IBAT inhibitor compounds. Again, an attempt is made to define the product (compounds in this case) by reference to a result to be achieved. It is thereby not clear as to what compounds are covered by this expression. Present claims 1-10 therefore do not fulfil the requirements of PCT art 6, which states that claims shall be clear and concise.

D2 describes oral controlled release pharmaceutical compositions. The compositions are designed to deliver the active medicinal ingredient at the desirable targeted site in the intestinal tract. Diltiazem hydrochloride, a benzothiazepine, is used in example 2. Diltiazem hydrochloride is structurally very similar to some of the compounds mentioned as examples of suitable IBAT inhibitor compounds in the present description.

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

Some benzothiazepines have an effect on the bile acid uptake according to D1. In col. 33, lines 27-49 and col. 34, lines 25-67, compositions comprising such IBAT-inhibitor compounds are described. The compositions are designed to deliver the active substance in a way of controlled release, such as enteric-coated tablets.
It is considered obvious for the skilled person, with the knowledge of the formulations in D1, to target the IBAT inhibitor compound to the ileum, when structurally similar compounds are known in formulations such as those in D2.

The use of certain bile acid binders is described in D3. The problem connected with diarrhoea induced by an increased load of bile acids in the colon is minimised, using for example enterocoated cholestyramine, designed to be released in colon.

The effect of IBAT inhibitor compounds may lead to increased levels of bile acids in colon, which in turn could potentially generate diarrhoea. D3 presents a solution to the same problem. To combine an IBAT inhibitor compounds with a bile acid binder in a formulation, as in present claims 16-19, is therefore considered obvious for the skilled person. As IBAT inhibitor compounds are already used in treatment of hyperlipidaemic conditions, claim 21 is also considered to be obvious as well, to the skilled person.

Accordingly, claims 1-10,16-19 and 21 are therefore considered to fulfil the requirements of novelty, but are not considered to fulfil the requirements of inventive step. The claims 1-10,16-19 and 12 are considered to be industrially applicable.

VIII. Certain observations n the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The subject matter of claims 1-10 refers to oral pharmaceutical formulations comprising an inhibitor compound of the ileal bile acid transport (IBAT inhibitor compound). The formulation is designed to deliver the IBAT inhibitor compound in the ileum.
Present claims 1-10 are defined by reference to the desirable effect of the formulation, such as the target for delivery of the active substance or the lag time. The claims lack the technical features needed to bring about such effects. In the same claims 1-10 is included the expression IBAT inhibitor compounds. Again, an attempt is made to define the product (compounds in this case) by reference to a result to be achieved. It is thereby not clear as to what compounds are covered by this expression. Present claims 1-10 therefore do not fulfil the requirements of PCT art 6, which states that claims shall be clear and concise.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* H 2036-1 WO

Box No. I TITLE OF INVENTION

NEW PHARMACEUTICAL FORMULATIONS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

AstraZeneca AB
S-151 85 Södertälje
Sweden

☐ This person is also inventor.

Telephone No.
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Facsimile No.
+46 8 553 288 20

Teleprinter No.

State *(that is, country)* of nationality:
SE

State *(that is, country)* of residence:
SE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ABRAHAMSSON, Bertil
AstraZeneca R&D Mölndal
S-431 83 Mölndal
Sweden

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:
SE

State *(that is, country)* of residence:
SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Global Intellectual Property, Patents
AstraZeneca AB
S-151 85 Södertälje
Sweden

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Facsimile No.
+46 8 553 288 20

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LINDQVIST, Ann-Margret
AstraZeneca R&D Mölndal
S-431 83 Mölndal
Sweden

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: SE

State *(that is, country)* of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

UNGELL, Anna-Lena
AstraZeneca R&D Mölndal
S-431 83 Mölndal
Sweden

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: SE

State *(that is, country)* of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- [X] **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- [X] **AE** United Arab Emirates
- [X] **AL** Albania
- [X] **AM** Armenia
- [X] **AT** Austria
- [X] **AU** Australia
- [X] **AZ** Azerbaijan
- [X] **BA** Bosnia and Herzegovina
- [X] **BB** Barbados
- [X] **BG** Bulgaria
- [X] **BR** Brazil
- [X] **BY** Belarus
- [X] **CA** Canada
- [X] **CH and LI** Switzerland and Liechtenstein
- [X] **CN** China
- [X] **CR** Costa Rica
- [X] **CU** Cuba
- [X] **CZ** Czech Republic
- [X] **DE** Germany
- [X] **DK** Denmark
- [X] **DM** Dominica
- [X] **EE** Estonia
- [X] **ES** Spain
- [X] **FI** Finland
- [X] **GB** United Kingdom
- [X] **GD** Grenada
- [X] **GE** Georgia
- [X] **GH** Ghana
- [X] **GM** Gambia
- [X] **HR** Croatia
- [X] **HU** Hungary
- [X] **ID** Indonesia
- [X] **IL** Israel
- [X] **IN** India
- [X] **IS** Iceland
- [X] **JP** Japan
- [X] **KE** Kenya
- [X] **KG** Kyrgyzstan
- [X] **KP** Democratic People's Republic of Korea
- [X] **KR** Republic of Korea
- [X] **KZ** Kazakhstan
- [X] **LC** Saint Lucia
- [X] **LK** Sri Lanka
- [X] **LR** Liberia
- [X] **LS** Lesotho
- [X] **LT** Lithuania
- [X] **LU** Luxembourg
- [X] **LV** Latvia
- [X] **MA** Morocco
- [X] **MD** Republic of Moldova
- [X] **MG** Madagascar
- [X] **MK** The former Yugoslav Republic of Macedonia
- [X] **MN** Mongolia
- [X] **MW** Malawi
- [X] **MX** Mexico
- [X] **NO** Norway
- [X] **NZ** New Zealand
- [X] **PL** Poland
- [X] **PT** Portugal
- [X] **RO** Romania
- [X] **RU** Russian Federation
- [X] **SD** Sudan
- [X] **SE** Sweden
- [X] **SG** Singapore
- [X] **SI** Slovenia
- [X] **SK** Slovakia
- [X] **SL** Sierra Leone
- [X] **TJ** Tajikistan
- [X] **TM** Turkmenistan
- [X] **TR** Turkey
- [X] **TT** Trinidad and Tobago
- [X] **TZ** United Republic of Tanzania
- [X] **UA** Ukraine
- [X] **UG** Uganda
- [X] **US** United States of America
- [X] **UZ** Uzbekistan
- [X] **VN** Viet Nam
- [X] **YU** Yugoslavia
- [X] **ZA** South Africa
- [X] **ZW** Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- [X] DZ Algeria
- [X] AG Antigua and Barbuda

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn bythe applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application: * regional Office	international application: receiving Office
item (1) 19 April 1999 (19.04.1999)	9901387-2	Sweden (SE)		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one county party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* :

ISA / SE

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)*	Number	Country *(or regional Office)*
16 December 1999	SE99/00471	Sweden (SE)

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 4
description (excluding sequence listing part)	: 16
claims	: 3
abstract	: 1
drawings	:
sequence listing part of description	:
Total number of sheets	: 24

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any: no number assigned yet
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: ITS Report SE99/00471

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity isnot obvious from reading the request).

Södertälje, 19 April 2000

.....

Christer Wahlström
Global Intellectual Property, Patents, AstraZeneca AB

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 45/00, 9/20, A61P 3/06 — A1

(11) International Publication Number: **WO 00/62810**

(43) International Publication Date: 26 October 2000 (26.10.00)

(21) International Application Number: PCT/SE00/00755

(22) International Filing Date: 19 April 2000 (19.04.00)

(30) Priority Data:
9901387-2 19 April 1999 (19.04.99) SE

(71) Applicant *(for all designated States except US)*: ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ABRAHAMSSON, Bertil [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). LINDQVIST, Ann-Margret [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). UNGELL, Anna-Lena [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE).

(74) Agent: ASTRAZENECA AB; Global Intellectual Property, Patents, S-151 85 Södertälje (SE).

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: AN ORAL FORMULATION FOR ILEUM ADMINISTERING COMPRISING AN INHIBITOR COMPOUND OF THE ILEAL BILE ACID TRANSPORT

(57) Abstract

An oral pharmaceutical formulation comprising an inhibitor compound of the ileal bile acid transport (IBAT inhibitor compound) and a therapeutically acceptable carrier characterised in that the formulation is designed to deliver the IBAT inhibitor compound in the ileum. The IBAT inhibitor compound can also be administered in combination with a bile acid binder to alleviate possible side effects of therapy with IBAT inhibitor compound, such as for instance diarrhoea. The bile acid binder may be formulated for colon release.

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AN ORAL FORMULATION FOR ILEUM ADMINISTERING COMPRISING AN INHIBITOR COMPOUND OF THE ILEAL BILE ACID TRANSPORT

FIELD OF THE INVENTION

The present invention relates to an oral pharmaceutical dosage form comprising a substance with inhibiting effect on the ileal bile acid transport system (IBAT). More specifically, the dosage form is suitable in the treatment of hypercholesterolaemia. The invention also relates to manufacturing processes and the use of the dosage form in the treatment of hypercholesterolaemia. A further aspect of the invention is the use of a substance with inhibiting effect on IBAT in combination with a bile acid binder by simultaneously, separately or sequentially administration of the two substances, and the use of these substances in the manufacture of such a pharmaceutical dosage form.

BACKGROUND OF THE INVENTION AND PRIOR ART

It is well known that hyperlipidemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol are major risk factors for coronary heart disease and particularly artherosclerosis. Interfering with the circulation of bile acids within the lumen of the intestinal tracts is found to reduce the level of cholesterol. Previous established therapies to reduce the concentration of cholesterol involve for instance treatment with HMG-CoA reductase inhibitors, preferably statins such as simvastin and fluvastin, or treatment with bile acid binders, such as resins. Frequently used bile acid binders are for instance cholestyramine and cholestipol. One recently proposed therapy involves the treatment with substances with inhibiting effect on the ileal bile acid transport system (IBAT).

Re-absorption of bile acid from the gastro-intestinal tract is a normal physiological process, which mainly takes place in the ileum by an active transport mechanism called ileal bile acid transport (IBAT). Inhibitors of IBAT can be used in the treatment of hypercholesterolaemia. See for instance "Interaction of bile acids and cholesterol with

nonsystemic agents having hypocholesterolemic properties", Biochemica et Biophysica Acta, 1210 (1994) 255- 287. Thus, suitable compounds having such inhibitory IBAT activity are also useful in the treatment of hyperlipidaemic conditions.

Several chemical compounds possessing such IBAT activity have recently been described, see for instance hypolipidaemic benzothiazepine compounds described in International Patent Application, Publication No. WO 93/16055 and WO 96/16051; condensed 1,4-thiazepines described in International Patent Application, Publication No. WO 94/18183; different heterocyclic compounds described in International Patent Application, Publication No. WO 94/18184; and 1,4-benzothiazepine-1,1-dioxides described in International Patent Application, Publication No. WO 96/05188, all of which are hereby incorporated by reference.

Further, especially suitable compounds for the present invention are for instance benzothiazepines with IBAT activity described in International Patent Application, Publication No. WO 96/08484; bile acid resorption inhibitors described in International Patent Application, Publication No. WO 97/33882, WO 98/07449 and WO 98/03818, and in European Patent Application, Publication No. EP-A-0864582, EP-A-0489423, EP-A-0549967, EP-A-0573848, EP-A-0624593, EP-A-0624594, EP-A-0624595, and EP-A-0624596, all of which are hereby incorporated by reference. Further compounds of interest can be found in International Patent Application, Publication No. WO 99/32478, WO 99/64409 and WO 00/01687, all of which are hereby incorporated by reference.

It is proposed that these types of compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals. For instance, the dosage forms can be a daily dose which is administered once a day or being divided to be administered several times a day, or alternative in a sustained release form. Suitable dosage forms are intended for oral administration.

All benzothiazepines, however, will not be effective as IBAT inhibitor compounds. Thus, diltiazem, which is a 1,5-benzothaizepine, is a calcium blocker with coronary vasodilating activity (see The Merck Index, Merck & Co, Inc., 12th ed., 1996, p. 541). With respect to inhibition of IBAT, diltiazem has no activity.

In general, pharmaceutical drug substances will be absorbed in the upper small intestine, and therefore only a small amount will reach ileum when administered in a conventional oral dosage form. Irrespective of the construction of the pharmaceutical dosage form, it should provide contact for the active compound, e.g. inhibitor of IBAT, with the compound´s site of action in the body, for example in the ileum. The above prior art documents discuss in general terms suitable pharmaceutical dosage forms for the described IBAT inhibitor compounds. However, none of the documents describe a specific way to obtain a release of the active substance directly to or close to the site of action.

Contact between the active drug and the site of action can be established in different ways. The present application describes a new pharmaceutical dosage form which reduces and minimises absorption, metabolism and dilution in the luminal content of the IBAT inhibitor in the body before the active substance (IBAT inhibitor compound) reaches its site of action.

It has been proposed that after absorption over the gastro-intestinal membrane, an IBAT inhibitor could interact with transport systems similar to IBAT for instance the corresponding transport system in the liver (LBAT) or could provide other non-specific systemic effects which could lead to undesirable pharmacological or even toxicological effects. This could severely limit the clinical usefulness of IBAT inhibitors especially in the treatment of hypercholesterolaemia, i.e. conditions associated with elevated concentra-tions of total cholesterol and low-density lipoprotein cholesterol.

The inhibition of the re-absorption of bile acids from the small intestine performed by an effective IBAT inhibitor may lead to increased levels of bile acids in the lower parts

(colon) of the gastro-intestinal tract. Such an increase of bile acid concentrations in the distal regions could potentially generate diarrhoea and discomfort to the patient. The present invention provides a new approach to minimise the concentration of free bile acids in the colon and thereby reduce the potential risk of adverse events by co-administration of a bile acid binder together with the IBAT inhibitor. However, the combination of an IBAT inhibitor and a bile acid binder have previously been proposed in the above patent applications describing new IBAT inhibitor compounds. The purpose of such previously described combinations have been to enhance the cholesterol lowering efficacy of the therapy, and there is no hint that such a combination could be used to minimise a potential risk for diarrhoea connected with IBAT inhibitor therapy.

BRIEF DESCRIPTION OF THE INVENTION

The aim of the present invention is to reduce the problem with undesirable side effects of IBAT inhibitor compounds by providing a pharmaceutical formulation, which reduces the systemic drug exposure while maintaining or enhancing the cholesterol lowering effect of the drug. Such undesirable systemic effects put a load on other organs, e.g. liver and kidneys. Thus, the present dosage form provides a reduced, i.e. minimum absorption, metabolism and dilution in the luminal content of the IBAT inhibitor by a specific targeting to the site of action. The release is directed specifically to the site of action which reduces or even might avoid toxicological effects of the drug. The formulation is intended to be orally administered and pass through the upper part of the small intestine with a minimum release of the IBAT inhibitor before it reaches the distal jejunum or proximal ileum.

The present invention provides such a dosage form, which delivers the main part of the dose to the site of action, i.e. in the distal jejunum, in the proximal ileum or in the distal ileum. The release of the drug is thereby reduced or minimised to more proximal parts, the duodenum and jejunum, where drug absorption in general is most efficient. Thus, the

release of the drug should preferably start in the distal jejunum or proximal ileum, or the entire dose should be delivered directly to the ileum.

Preferably, the formulation is an orally administered formulation, such as a delayed release formulation, which starts to release the main part of the drug in the distal jejunum or in the proximal ileum. The oral formulation might also provide protection of the drug from the acid environment in the stomach by an enteric coating. Such an enteric coating also protects the gastric mucosa from drug exposure and thereby minimises irritation or even damages of the gastric mucosa potentially caused by aggressive drug exposure.

An additional aim of the present invention is to provide a combination for simultaneous, separate or sequential administration which combination comprises an IBAT inhibitor and a bile acid binder. Such a combination will protect the patient from any possible side effect caused by excess of bile acids in the colon, such as diarrhoea. If the transport of bile acids is blocked by an IBAT inhibitor the bile acids might be deposited in the colon and induce a secretory diarrhoea - by irritation and inflammation - as a undesired side effect caused by the treatment with an IBAT inhibitor.

Another aspect of the provided combination therapy is that the bile acid binder, for instance a resin such as cholestyramine or cholestipol, could preferably be administered in a dosage form with colon release of the bile acid binder. A colon release formulation will provide protection of the bile acid binder to the luminal contents in the more proximal parts of the intestine, where the bile acid concentrations are high. Such a formulation will prevent binding of bile acids to the bile acid binder before the formulation reaches the colon. Thereby, maximal bile acid binding capacity will be obtained in the colon and any possible gastro-intestinal side effects, such as diarrhoea, may be avoided. Thus, any additional amount of bile acid presented in the colon due to the treatment with the IBAT inhibitor compound, would be bound to a bile acid binder, which the bile acid binder is preferably delivered in the colon, thereby any possible side effects such as diarrhoea is avoided.

DETAILED DESCRIPTION OF THE INVENTION

IBAT inhibitor compounds

Active ingredients suitable as IBAT inhibitor compounds in the present invention are those exhibiting activity when screening for IBAT inhibiting properties. Suitable examples of such compounds can be found in the references cited on page 2 of the present application.

Active ingredients particularly suitable as IBAT inhibitor compounds in the present invention include benzothiazepines, and more particularly 1,4-benzothiazepines and 1,5-benzothiazepines exhibiting activity when screening for IBAT inhibiting properties. Of these, compounds with an oxidized sulfur group, particularly a sulfone group, in the 7 membered ring are preferred. Furthermore, the presence of an amine group in the 7 membered ring is preferred.

Pharmaceutical formulations

According to one aspect of the invention, an orally administered pharmaceutical formulation of an IBAT inhibitor compound is provided, which formulation releases almost the entire dose of the IBAT inhibitor compound in the distal jejunum, in the proximal ileum, or deliver the dose directly to the ileum. Such a formulation will minimise drug release in the upper part of the small intestine, i.e. above distal jejunum.

Optimal drug release and drug binding in the ileum can for instance be obtained by a delayed release formulation, such as a formulation with a specified lagtime. More specifically, less than 30 % of the drug could be released during the time the formulation spends in the stomach and in the proximal small intestine, i.e. during the passage of the upper part of the small intestine.

Thus, according to a second aspect, the present invention provides a pharmaceutical formulation with a delayed release of the IBAT inhibitor compound by a controlled lagtime. The main part of the formulation shall pass the duodenum and jejunum with a minimum release of the active dose, and thereby increasing the dose available for binding to the site of action in the ileum and thereby increasing the inhibition of the ileal bile acid transport system. Preferably, the lagtime period is about 0.5 - 2 hours calculated from emptying from the stomach, and more than 70 % of the dose should be released approximately during the next 0.5 - 2.0 hours, i.e. after the lagtime period. More preferably, the dose should be released during the first hour after the lagtime period.

Dosage forms with a controlled lagtime can be constructed in different ways for instance as described in the following.

A controlled lagtime can be triggered by pH changes, redox potential differences or luminal metabolic changes in the gastro-intestinal tract as described in Aliment Pharmacol Ther 1997, 11 (suppl 3): 109-115. Such a controlled lagtime could be obtained for instance by a programmed disintegration of the formulation due to erosion, dissolution or in general by components present in the formulation interacting with the environment in the gastro-intestinal tract. Preferably, the drug release from the dosage form could be triggered by the pH variation between jejunum and ileum.

Alternatively, the drug release from the dosage form can be chronographic controlled to obtain the above specified time limits, such as for instance described in the European Patent Application, Publication No. EP-A-0384642.

When the formulation reaches the distal jejunum or the ileum, the drug release should preferably be either immediately, with a sustained release or be based on a combination of such release principles. The duration of the drug release for a sustained release formulation should preferably not exceed 2 hours.

According to a third aspect of the invention, a sustained release formulation can be constructed by any known principle, such as eroding or non-eroding matrices, membrane-coating layers or by diffusion or osmotically driven drug release. Suitable techniques for the construction of such formulations are for instance described in M. E. Aulton, Pharmaceutics, The science of dosage form design. (1988).

An additional aspect of the invention is to combine an IBAT inhibitor compound with a bile acid binder thereby avoiding a possible risk of excess of bile acids in colon caused by the inhibition of the ileal bile acid transport system. An excess of bile acids in the visceral contents may cause diarrhoea. Thus, the present invention also provides a treatment of a possible side effect such as diarrhoea in patients during therapy comprising IBAT inhibitor compounds.

Suitable bile acid binders for such a combination therapy are resins, such as cholestyrmine and cholestipol. One advantage is that the dose of bile acid binder might be kept lower than the therapeutical dose for treatment of cholesterolemia in single treatment comprising solely a bile acid binder. By a low dose of bile acid binder any possible side effects caused by poor tolerance of the patient to the therapeutic dose could also be avoided.

A further aspect in connection with such a combination therapy is that the bile acid binder could be administered in a dosage form with colon release, i.e. delivery of the active dose of bile acid binder in the colon. A possible risk of receiving an excess of bile acid in the colon by treatment with an IBAT inhibitor could be avoided by co-administration of a bile acid binder with colon release. Thus, any excess of bile acid in the colon, with a possible risk to cause diarrhoea, will be bound into a resin. The dose of the bile acid binder could be kept low due to an effective use of the dose by such a colon release. The colon delivery of the bile acid binder can be obtained by a formulation comprising a core containing the bile acid binder and optionally pharmaceutically acceptable excipients, and a coating of said core with a delayed release membrane adapted for colonic delivery. Technologies to obtain

such a delivery of drugs to the colon are for example described in Drug Development and Industrial Pharmacy 1997, 23: 893-913.

Further general aspects of the invention are that the formulations can be solid, semi-solid or liquid formulations. In a solid formulation, the carrier can be monolithic, such as tablets or capsules. One preferred monolithic formulation is a coated tablet, a capsule comprising small, coated units or a multiple unit tablet comprising a multitude of small coated units. Semi-solid or liquid formulations can be administered in capsules suitable for such vehicles. The most preferred formulation is an oral formulation such as a tablet or a capsule comprising coated small units or pellets. The formulation or dosage form may contain from 0.05% to 95% of the active compound in admixture with a pharmaceutically acceptable carrier, or pharmaceutically acceptable excipients.

Preparation of core material

The core material for the units, i.e. the tablets or the individual pellets can be constituted according to different principles. The core material may be homogenous or heterogeneous. The core containing the active principle may be differently formulated such as monolithic tablets, capsules, granules, pellets, other particles or crystals.

With a homogenous core material is meant, that it has a homogenous distribution of active substance throughout the core material.

The active substance, i.e. the IBAT inhibitor compound, is optionally mixed with further components to obtain preferred handling and processing properties and a suitable concentration of the active substance in the final mixture. Such components can be binders, surfactants, lubricants, glidants, fillers, additives or other pharmaceutically acceptable ingredients, alone or in mixtures.

Said core material may be produced either by direct compression of the mixed ingredients, or by granulation of the ingredients followed by compression of the granulated material.

In direct compression, the ingredients are mixed and compressed by using ordinary tableting equipment.

For the granulation there are numerous alternatives of granulating procedures mentioned in the literature, dry methods like roller compaction (Chilsonator) and wet methods utilizing granulating solutions with and without the addition of binders. A variant of the wet methods is to make a spray-granulation in a fluid bed.

For the wet granulating methods, either organic solvents, aqueous solutions or pure water may be utilized to prepare the granulating solutions. Due to environmental considerations pure water is preferred, if it is possible due to the composition of the mixture.

Homogenous core particles can also be prepared by techniques such as dry or wet milling, freeze milling, air-jet micronisation, spray drying, spray chilling, controlled crystallisation, supercritical crystallisation, emulsion solvent evaporation and emulsion solvent extraction.

The core material may also be produced by extrusion/spheronization, balling or compression, utilizing different process equipments.

The size of the formulated core materials is approximately between 2 and 14 mm, preferably between 3 and 9 mm for a tablet preparation, and between 0.001 and 4 mm, preferably between 0.001 and 2 mm for a pellet preparation.

The manufactured core material may be further layered with additional ingredients comprising the active substance and/or be used for further processing.

Alternatively, the core material may be heterogeneous with an inner zone, for instance a seed or sphere, not containing the active substance. A layer comprising the active

substance, and optionally pharmaceutically acceptable excipients, surrounds this seed or sphere.

The seed or sphere may be soluble or insoluble. Optionally, the seed or sphere (inner zone) may be coated with an inert layer to prepare a smooth surface before the layer containing active substance is applied onto the seed/sphere.

Insoluble seeds/spheres may comprise different oxides, celluloses, organic polymers and other materials, alone or in mixtures. Water-soluble seeds/spheres may comprise different inorganic salts, sugars and other materials, alone or in mixtures. The size of the seeds may vary between approximately 0.1 and 2 mm. The seeds layered with the matrix containing the active substance are produced either by powder or solution/suspension layering using for instance granulating or spray coating/layering equipment.

Processes for application of delayed release membranes

Delayed release membrane can be applied to the core material, being a monolithic tablet, multiple units or a hard or soft gelatine capsule, by coating or layering procedures in suitable equipment such as coating pans, coating granulators or in a fluidized bed apparatus using water and/or organic solvents for the coating process. Also powder-coating principles may be applied. Another possibility is to apply the coating by microencapsulation techniques such as coacervation, emulisification with subsequent removal of the solvent by extraction or evaporation, ionotropic gelation or congealing.

Such delayed release membranes may be applied on core material comprising the IBAT inhibitor for delivery to the distal small intestine and optionally also be applied to the bile acid binder for delivery to the colon.

Pharmaceutical additives

Delayed release coatings may be obtained by one or more, separetely or in compatible combinations of pharmaceutically acceptable ingredients, in amounts carefully titrated to reach the intended release properties. As coating layer, the following pH sensitive polymers can be applied; e.g. methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethyl ethyl-cellulose, shellac or other suitable enteric coating layer polymer(s). The coating layer may also be composed of film-forming polymers being sensitive to other luminal components than pH, such as bacterial degradation or a component that has such a sensitivity when it is mixed with another film-forming polymer. Examples of such components providing delayed release to the intended regions are; polymers comprising azo bond(s), polysaccharides such as pectin and its salts, galactomannans, amylose and chondroitin, disulphide polymers and glycosides.

The delayed release coating or an additional coating of the formulation may contain other film-forming polymers being non-sensitive to the luminal conditions for technical reasons or chronographic control of the drug release. Materials to be used for such purpose includes, but are not limited to; sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures.

Additives such as dispersants, colorants, pigments, additional polymers e.g. poly(ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the coating layer. Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the core material.

The coating layers may also contain pharmaceutically acceptable plasticizers to obtain desired mechanical properties. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, glycerol monoesters, polysorbates or other plasticizers and mixtures thereof. The amount of plasticizer is preferably optimised for each formula, in relation to the selected polymer(s), selected plasticizer(s) and the applied amount of said polymer(s).

In preparation of tablets, either as monolithic drug containing cores for subsequent coating with a delayed release membrane or as a matrix for coated multiple units, additional ingredients may be needed to obtain suitable technical properties such as binders, disintegrants, bulk agents, glidants, lubricants, and coatings agents without effects on the drug release such as water soluble polymers, anti-tacking agents, colourants, pigments and waxes. Ingredients well known for such usage are for example described in "Handbook of pharmaceutical excipients", 2nd edition, 1994, Pharmaceutical Press, London.

Preparation of final dosage forms

Coated units may be filled into hard gelatine capsules or mixed with tablet excipients, such as fillers, binders, disintegrants, lubricants and other pharmaceutically acceptable additives, and be compressed into tablets. The compressed tablet is optionally covered with film-forming agents to obtain a smooth surface of the tablet and further enhance the mechanical stability of the tablet during packaging and transport. Such a tablet coat, which may be applied on a multiple unit tablet or a conventional tablet, may further comprise additives like anti-tacking agents, colourants and pigments or other additives to improve the tablet appearance.

Suitable drugs for the new formulations are IBAT inhibitor compounds such as described in the above-discussed documents, hereby incorporated by references.

The IBAT inhibitor compound could alternatively be a low permeability drug as defined in the Biopharmaceutical Classification System proposed by FDA.

A combination therapy according to the invention should preferably comprise simultaneously, separately or sequentially administration of an IBAT inhibitor compound and a bile acid binder. The IBAT inhibitor could preferably be formulated for ileum delivery and the bile acid binder could preferably be formulation for colon release.

Medical and pharmaceutical use of the invention

The pharmaceutical formulations according to the present invention can be used in the treatment of hypercholesterolaemia. A suitable unit dose will vary with respect to the patients body weight, condition and disease severity. The dose will also depend on if it is to be used for prophylaxis or in the treatment of severe conditions, as well as the route of administration. The daily dose can be administered as a single dose or divided into two or more unit doses. An orally administered daily dose of an IBAT inhibitor is preferably within 0.1 – 1,000 mg, more preferable 1 - 100 mg.

A pharmaceutical formulation according to the present invention with a targeted delivery in the gastro intestinal tract provides a reduced systemic exposure, as can be measured by the area under the drug plasma concentration versus time curve (AUC), while maintaining or even increasing the therapeutic effect, as e.g. measured by serum cholesterol reduction.

A combination therapy comprising an IBAT inhibitor and a bile acid binder comprises preferably a low daily dose of the bile acid binder, such as less than 5 g of a resin, and more preferably less than 2 g. A dosage form with colon release of the bile acid binder could be constructed by any of the above described principles for delayed release formulations.

The following contemplated Examples are intended to illustrate, but in no way limit the scope of the invention.

EXAMPLES

Example 1

A formulation having the following composition can be prepared:

	amount/capsule (mg)
IBAT inhibitor compound (1,5-benzothiazepine)	10
Non pareil spheres	500
Ethyl cellulose	2
Hydroxypropylmethyl cellulose	10
Eudragit L100-55	25
Triethylcitrate	2.4

The active drug can be dissolved together with ethyl cellulose and hydroxypropyl cellulose in ethanol 99 %. The mixture can then be sprayed onto the non-pareil spheres in a fluidized bed apparatus. Thereafter, the pellets can be dried and aerated to remove residual ethanol. The Eudragit L100-55 dispersion with addition of triethyl citrate can then be sprayed onto the drug beads in a fluidized bed apparatus. Subsequently, the coated beads can be filled in hard gelatine capsules after drying and sieving.

Example 2

A formulation having the following composition can be prepared:

	amount/tablet (mg)
IBAT inhibitor compound (1,5-benzothiazepine)	10
Silicon dioxide	200
Povidone K-25	20
Eudragit FS30D	30
Microcrystalline cellulose	250
Sodium stearyl fumarate	5

The active drug can be suspended in water and sprayed onto silicon dioxide cores of a predefined size in a fluidized bed apparatus. The drug pellets can be dried in an oven at 40° C for 24 h. Thereafter, a layer of Povidone K-25 can be applied on the beads from an ethanolic solution in a fluidized bed apparatus. A final coat of Eudragit FS30D dispersion can be applied thereafter in a fluidized bed. The coated beads can be mixed with microcrystalline cellulose and sodium stearyl fumarate in a mixer and subsequently compressed to tablets.

CLAIMS

1. An oral pharmaceutical formulation comprising an inhibitor compound of the ileal bile acid transport (IBAT inhibitor compound) and a pharmaceutically acceptable carrier, wherein the formulation is designed to deliver the IBAT inhibitor compound in the ileum.

2. The oral pharmaceutical formulation according to claim 1, wherein the formulation is designed to deliver the IBAT inhibitor compound in the ileum by release in one or more parts of the body selected from the distal jejunum and proximal ileum, and/or directly in the ileum.

3. The formulation according to claim 1, wherein the carrier is designed to deliver the IBAT inhibitor compound in the ileum.

4. The formulation according to claim 1, wherein the carrier is designed to release the IBAT inhibitor compound in the distal jejunum and in the proximal ileum.

5. The formulation according to any one of the claims 1 to 4, wherein the carrier is designed to give a minimum release of the IBAT inhibitor compound in the upper part of the small intestine.

6. The formulation according to any one of claims 1 to 4, wherein the pharmaceutical formulation is a delayed release formulation.

7. The formulation according to claim 6, wherein the formulation provides a lagtime of about 0.5 - 2 hours after emptying the stomach.

8. The formulation according to claim 7, wherein the IBAT inhibitor compound is released during the first hour after the lagtime.

9. The formulation according to claim 6, wherein release of the IBAT inhibitor compound from the delayed release formulation is triggered by the pH differences between the jejunum and ileum.

10. The formulation according to any one of claims 1 to 9, wherein the IBAT inhibitor compound is a low permeability drug as defined in the Biopharmaceutical Classification System FDA.

11. The use of a pharmaceutical formulation comprising an IBAT inhibitor compound with targeted delivery in the gastro-intestinal tract according to any one of the claims 1 to 10 to reduce systemic exposure.

12. The use of a pharmaceutical formulation comprising an IBAT inhibitor compound with targeted delivery in the gastro-intestinal tract according to any one of the claims 1 to 10 to enhance the therapeutic effect.

13. The use of a pharmaceutical formulation according to any one of the claims 1 to 10 in the treatment of hypercholesterolemia.

14. The use of a pharmaceutical formulation according to any one of the claims 1 to 10, in the manufacture of a medicament for the prophylactic or therapeutic treatment of hypercholesterolemia.

15. A method for prophylactic or therapeutic treatment of a subject suffering from, or susceptible to, hypercholesterolemia, which method comprises administering to the subject a pharmaceutical formulation designed according to any one of claims 1 to 10.

16. A pharmaceutical formulation for simultaneous, separate or sequential administration in the prophylactic or therapeutic treatment of hypercholesterolemia, which formulation comprises an IBAT inhibitor compound and a bile acid binder.

17. The pharmaceutical formulation according to claim 16, wherein the IBAT inhibitor compound is a low permeability drug as defined in claim 10.

18. The pharmaceutical formulation according to claim 16, wherein the bile acid binder is a resin.

19. The pharmaceutical formulation according to claim 18, wherein the bile acid binder is in a formulation with colon release.

20. The use of a pharmaceutical formulation according to any one of claims 16 - 19 in the treatment of diarrhoea during therapy comprising an IBAT inhibitor compound.

21. The use of a pharmaceutical formulation according to any one of the claims 16 to 20, in the manufacture of a medicament for the prophylactic or therapeutic treatment of hypercholesterolemia.

22. A method for prophylactic or therapeutic treatment of a subject suffering from, or susceptible to, diarrhoea during therapy comprising an IBAT inhibitor compound, which method comprises administering to the subject a pharmaceutical formulation designed according to any one of claims 15 to 18.

23. The use of a bile acid binder as prophylaxis or in the treatment of diarrhoea during therapy comprising an IBAT inhibitor compound.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/00755

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 45/00, A61K 9/20, A61P 3/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5614220 A (YOSHIYUKI HIRAKAWA ET AL), 25 March 1997 (25.03.97) --	1-23
X	US 5723458 A (LAWRENCE EDWARD BRIEADDY ET AL), 3 March 1998 (03.03.98) --	1-23
A	Dialog Information Services, File 73, EMBASE, Dialog accession no. 02888148, Embase accession no. 1985132107, Jacobsen O. et al: "Effect of entercoated cholestyramine on bowel habit after ileal resection: A double blind crossover study"; & British Medical Journal (BR. MED. J.) (United Kingdoms) 1985, 290/6478 (1315-1318) -- --------	1-23

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 July 2000	03 -08- 2000
Name and mailing address of the ISA/ Swedish Pat nt Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson/gh Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/00755

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11-15,20,22-23
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/00755

Claims 11-15,20,22-23 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/SE 00/00755

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CN 1116926 A	21/02/96
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